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10/723,520	11/26/2003	Mark R. Andersen	4944 US	8934

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LIFE TECHNOLOGIES CORPORATION
C/O INTELLEVATE
P.O. BOX 52050
MINNEAPOLIS, MN 55402

EXAMINER	
PANDE, SUCHIRA	
ART UNIT	PAPER NUMBER
1637	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,520	ANDERSEN ET AL.	
	Examiner	Art Unit	
	SUCHIRA PANDE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,5,6,8-18,22,23 and 43-45* is/are pending in the application.

4a) Of the above claim(s) *10-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,5,6,8,9,22,23 and 43-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 7, 2009 has been entered.

Claim Status

2. Applicant has cancelled claims 1, 4, 7, 19-21 and 24-42; withdrawn claims 10-18; amended claims 2, 3, 5, 6, 8, 9, 22, 23, 43, 44 and added new claim 45. Currently claims 2, 3, 5, 6, 8, 9, 22, 23, 43, 44 and 45 are active and will be examined in this action.

Response to Arguments

Re 112 1st par. rejection of claims 1-3, 5-6, 8-9, 22-23, 43 and 44

3. Applicant has cancelled claim 1 and added new claim 45. All remaining claims depend from new claim 45. The new claim 45 does not recite "each of which is disposed between the ninety-five to one-thousand and thirteen primer sets amplifying a given target gene sequence of interest,". Hence the 112 1st NEW MATTER rejection is being withdrawn.

Re 112 2nd par. rejection of claims 1-3, 5-6, 8-9, 22-23, 43 and 44

4. Applicant has cancelled claim 1 and added new claim 45. All remaining claims depend from new claim 45. The new claim 45 does not recite------each of which is disposed between the -----primer sets amplifying a given target gene sequence of interest, Hence the 112 2nd rejection is being withdrawn.

Re 103 rejection of claims 1-3, 5-6, 8-9, 22-23 and 44 over Unger et al. ; Wang et al.; Ohnishi et al.; Dolganov et al. and First et al.

5. Applicant's arguments with respect to claims 1-3, 5-6, 8-9, 22-23 and 44 have been considered but are moot in view of the new ground(s) of rejection. Applicant has cancelled claim 1 and added new claim 45. All remaining claims depend from new claim 45. The cited art does not teach all aspects of amended claims. Hence previously cited 103 rejection is withdrawn and new art is being cited to address all aspects of new claim 45.

Re 103 rejection of claim 43 over Unger et al.; Wang et al.; Ohnishi et al.; Dolganov et al. and First et al. as applied to claim 1 above, and further in view of Heid et al.

6. Applicant's arguments with respect to claim 43 have been considered but are moot in view of the new ground(s) of rejection. Applicant has cancelled claim 1 and added new claim 45. All remaining claims depend from new claim 45. The cited art does not teach all aspects of amended claim 45. Hence previously cited 103 rejection of claim 43 is withdrawn and new art is being cited to address all aspects of amended claim 43.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 45, 2, 5, 6, 8, 9, 43 and 44, are rejected under 35 U.S.C. 102(b) as being anticipated by Heid et al. (1996) Genome Research vol. 6 pp 986-994 (previously cited).

Regarding claim 45, Heid et al. teach a method for analyzing a sample (see page 993 par. 1 where total RNA is taught as a sample) or plurality of samples for the presence of one or more polynucleotide sequences of interest (see page 993 par. 2 where human factor VIII and β-actin genes are taught as polynucleotide sequences of interest), comprising:

(i) amplifying at least one of said polynucleotides derived from said sample (see page 986 par. 2 where PCR and reverse transcriptase PCR is taught. Also see page 993 par. 1 where primers for RT-PCR and F8for and F8rev primers are taught as PCR primers. Thus Heid et al. teach amplifying at least one of said polynucleotides derived from said sample) or said plurality of samples in the presence of:

(a) a plurality of different amplification primer pairs suitable for amplifying said polynucleotide sequences of interest (see page 993 par. 2 where F8for, F8rev---primers for factor VIII; and β-actin forward, β-actin reverse—primers for β-actin gene are taught as a plurality of different amplification primer pairs suitable for amplifying said polynucleotide sequences of interest); and

(b) a plurality of oligonucleotide probes, wherein each of said plurality of oligonucleotide probes is complementary to a region of a different polynucleotide sequence of interest amplified by said plurality of primer pairs and comprises a label suitable for monitoring amplification as a function of time (see page 993 par. 3 where F8probe and β-actin probes labeled with FAM and TAMRA are taught. These probes meet the criteria recited above namely a plurality of oligonucleotide probes, wherein each of said plurality of oligonucleotide probes is complementary to a region of a different polynucleotide sequence of interest amplified by said plurality of primer pairs and comprises a label suitable for monitoring amplification as a function of time); and

(ii) amplifying the products of said step (i) by performing real-time PCR (see page 993 par. 3 where real time PCR conditions are taught. Also see title where real-time PCR is taught. Thus teaching amplifying the products of said step (i) by performing real-time PCR) of in the presence of:

(a) at least one of said primer pairs used in step (i) (see page 993 par. 3 where each of factor VIII primer is used, thus teaching at least one of said primer pairs used in step (i)); and

(b) at least one of said oligonucleotide probes used in step (i) wherein said oligonucleotide probe in step (ii) is complementary to a region of a polynucleotide sequence of interest amplified by said primer pair in step (ii) (see page 993 par. 3 where F8probe is taught. Thus Heid et al. teach at least one of said oligonucleotide probes used in step (i) wherein said oligonucleotide probe in step (ii) is complementary to a region of a polynucleotide sequence of interest amplified by said primer pair in step (ii)).

Regarding claim 45, Heid et al. do not explicity recite dividing said products of step (i) into a plurality of aliquots and subsequently using at least one of said aliquots to perform the real –time PCR. However this teaching is inherent in the way the method of Heid et al. is designed. Heid et al. teach use both the primer sets for human factor VIII and β-actin along with their respective probes for real time amplification (see page 993 par. 3. Since both the probes for factor VIII and β-actin gene are identically labeled i.e. using FAM and TAMRA labels. In order to be able to follow the progress of each gene amplification by real time PCR the two pairs of primers and their respective FAM-TAMRA labeled probes have to be necessarily be present in different aliquots. Thus the method of Heid et al. is actually performed by dividing said products of step (i) into a plurality of aliquots and subsequently using at least one of said aliquots to perform the real –time PCR. Also see page 988 Fig. 1 where PCR product detection in real time is shown specially see Fig. 1B where amplification plots of serially (1:2) diluted human genomic DNA samples amplified with β-actin primers is taught. Thus by teaching real time detection of serially diluted human genomic DNA samples amplified with β-actin primers, Heid et al. inherently teach that the PCR product of step (i) is divided into plurality of aliquots for performing real -time PCR of at least one of said aliquots.

Thus all aspects of claim 45 are anticipated by Heid et al.

Regarding claim 2, Heid et al. teach method in which the amplification of step (i) is further carried out in the presence of a reverse transcriptase such that the polymerase chain reaction is reverse-transcription polymerase chain reaction and wherein the one or more polynucleotide sequences is obtained from mRNA derived

from the sample (see page 993 par. 1 where synthesis of cDNA for human factor VIII is taught starting from total RNA using RT PCR. The total RNA contains mRNA for human factor VIII which serves as a template for binding of the F8for and F8rev primers during the RT PCR reaction, thus Heid et al. teach method in which the amplification of step (i) is further carried out in the presence of a reverse transcriptase such that the polymerase chain reaction is reverse-transcription polymerase chain reaction and wherein the one or more polynucleotide sequences is obtained from mRNA derived from the sample).

Regarding claim 5, Heid et al. teaches a method in which the polymerase chain reaction of step (i) is carried out for a number of cycles such that the amplification remains in the linear range (see page 988 figure 1 panel A where amplification in linear range is taught).

Regarding claim 6, Heid et al. teaches a method in which the amplification in step (i) is achieved with a thermostable DNA polymerase (see page 993 par. 3 where thermostable Taq DNA polymerase is taught).

Regarding claim 8, Heid et al. teaches a method in which the label is a fluorophore. (see page 987 par. 3 where FAM a fluorophore is taught as label).

Regarding claim 9, Heid et al. teaches a method in which said plurality of oligonucleotide probes is selected from the group consisting of 5'-exonuclease probes, stem- loop beacon probes and stemless beacon probes. (see page 987 par. 3-4 where 5'-Taqman exonuclease probes that are based on 5' nuclease activity of Taq polymerase are taught).

Regarding claim 43, Heid et al. teaches method in which the amplification is carried out in the presence of uracil N-glycosylase (see page 993 par. 3 where AmpErase uracil N-glycosylase is taught).

Regarding claim 44, Heid et al. teaches in which the amplifying the at least one polynucleotide sequences comprises as many as fourteen PCR cycles (see page 993 par. 4 where 40 PCR cycles are taught, by this teaching Heid et al teach a method comprising as many as fourteen PCR cycles).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 3, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heid et al. as applied to claim 45 above further in view of Dolganov et al. (2001) Genome Research 11:1473-1483 (previously cited).

Regarding claim 3, Heid et al. teach method of claim 45 above, but do not teach a method in which the one or more polynucleotide sequences comprise a cDNA library.

Regarding claim 3, Dolganov et al. teach a method in which the one or more polynucleotide sequences comprise a cDNA library (see page 1474 where 34 genes of varying abundance in the sample were reverse transcribed and the RT-PCR products were cloned into pCRII-TOPO vector is taught. Thus Dolganov et al. teach a method in which the one or more polynucleotide sequences comprise a cDNA library).

Regarding claims 22 and 23, Dolganov et al. teach a method in which an observed efficiency of amplification is greater than 70%--claim 22 and in which an observed efficiency of amplification is greater than 90%--claim 23 (Dolganov et al. teaches a method in which relative transcript number of 75 genes from Asthmatic patients were compared to the healthy subjects as shown in page 1478-1479 Table 2, a huge range of expression levels are determined ranging from as high as 40 fold to as low as 0.223. These comparisons are based on the expression levels of same gene in the two subject populations. However, expression level of any given gene can be chosen as a base line and genes with expression level above that or below that cut off percentage can be determined. Thus Dolganov et al. teaches any selected range can be chosen as a cutoff. Thereby Dolganov et al. teaches selected level is 70% (claim 22) and selected level is 90% (claim 23).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Dolganov et al. in the method of

Heid et al. The motivation to do so is provided to one of ordinary skill by both Heid et al. and Dolganov et al.

Heid et al. state "we have developed a novel " real time" quantitative PCR method. The method measures PCR product accumulation through a dual-labeled fluorogenic probe (i.e., Taq Man Probe). This method provides very accurate and reproducible quantitation of gene copies. Unlike other quantitative PCR methods, real time PCR does not require post-PCR sample handling, preventing potential PCR product carry-over contamination and resulting in much faster and higher throughput assays (see abstract)."

Dolganov et al. state "Here we report a novel real-time PCR-based method specifically designed for quantification of multiple low abundance transcripts using as little as 2.5 fg of total RNA per gene. This method of gene expression profiling has the same specificity and sensitivity as RT-PCR and a throughput level comparable to low density DNA microarray hybridization. In this two-step method, multiplex RT-PCR is successfully combined with individual gene quantification via-real-time PCR on generated cDNA product." (see abstract).

Thus based on the above specific teachings one of ordinary skill in the art would have been motivated to practice the method of Dolganov et al. in the method of Heid et al. with a reasonable expectation of being able to perform quantification of multiple low abundance transcripts using as little as 2.5 fg of total RNA per gene as starting material and then performing individual gene quantification via-real time PCR on generated cDNA product.

Conclusion

11. All claims under consideration 45, 2, 3, 5, 6, 8, 9, 22, 23, 43 and 44 are rejected over prior art.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande
Examiner
Art Unit 1637

/Suchira Pande/
Examiner, Art Unit 1637